MODERN ANTIPYRETICS

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THE

MODERN ANTIPYRETICS:

THEIR ACTION

IN

HEALTH AND DISEASE.

BY

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PREFACE.

The presentation of new facts to the profession is chiefly the origin of this small volume.

A resumé of the properties of the coal-tar products used in medicine is also a want not fully supplied.

Isaac Ott.

Easton, Pa., Jan. 26, 1891.

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FEVER.

It is necessary to understand what fever is before we undertake the study of agents which reduce it. The process of fever is one of absorbing interest during every period of a physician's life. The constant level of temperature in man is accounted for by two theories: one that it is due to changes in heat production; the other, held by a minority, that it is kept so by changes in heat dissipation under the varying conditions of external temperature, changes in heat production playing a subordinate rôle. It is, as a rule, true that fever is primarily set up by an increase of heat production beyond that of heat dissipation; but when this is once established, the fever continues, not from excessive production, but from an altered relation between heat production and heat dissipation. All the recent researches go to show that fever is not a fire which is kept up by an excessive oxidation of the constituents of the human body. Perhaps I cannot better explain it than by the following comparison of MacAlister's:

Suppose a tall vessel containing water, the level of the water representing temperature. Let two pipes be connected with this vessel, one conveying water, the other carrying it off. Let the inlet and exit tubes be each provided with a stop-cock, and let the two stop-cocks be connected by a rigid link which insures that they always turn together and by the same amount. If to start with, the inflow and outflow are equal, then, however I move the linked stop-cocks, the height of the water will be the same. Now remove the rigid link, and connect the stop-cocks by a spiral spring. If now you move the inflow stop-cock so as to increase the flow, the outflow one will not at once follow, and, the balance being broken, the level of water will rise. But shortly the elasticity of the spring comes into activity, the outflow is equal to the inflow, and the rise will cease, but the new high level will be maintained. Every movement of either stop-cock will affect the level, which will fluctuate accordingly, but its height at any moment will not be an index of the amount of inflow at that moment. The inflow may be slight

while the level is high. If now you substitute heat production for inflow and heat dissipation for outflow, the rigid link will represent the healthy thermotaxic mechanism, then when this is weakened or relaxed or broken the steadiness of the normal level is impossible.

This view is still further supported by experiments upon animals. In (Exp. 9) Fig. 1 is a delineation of the access of fever, it having been studied during the first three hours and at intervals afterward. It shows after the injection per jugular of two drops of putrid blood that the heat production rises rapidly and attains its height some hours before the fever curve reaches its height. At the same time the curve of heat dissipation is lagging behind the curve of heat production, although following it in its upward ascent. In (Exp. 1) Fig. 1, there is an illustration of high temperature, although heat production and heat dissipation have fallen below normal of the

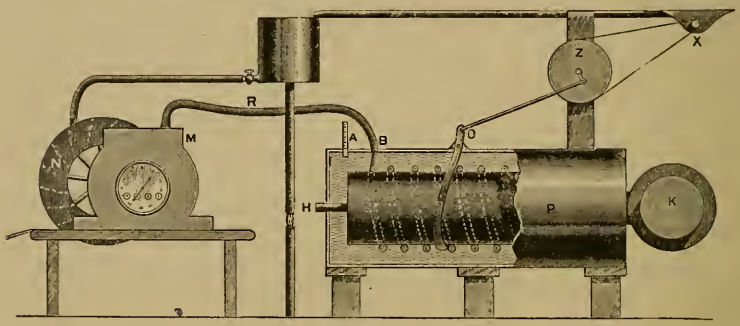

FIG. 2.

hunger or second day. It will be observed normally and during fever that the amount of heat production is fluctuating.

These views are also corroborated by an experiment upon a man afflicted with malarial fever. I shall give in detail the observations made with my human calorimeter:

It is composed of two cylinders of galvanized iron—one smaller than the other and enclosed within it (Fig. 2). The space in which the man lies upon a mattress is six feet long and two feet in diameter. Air is conveyed to him through the tube H (to which is attached at its inner end a coiled leaden tube through which the air enters the instrument), and traverses the whole length of the apparatus and enters the hollow tube of lead at P, and finally emerges at B, having given off its heat to the water between the two cylinders. The meter M is run by the water-wheel N which aspirates the water

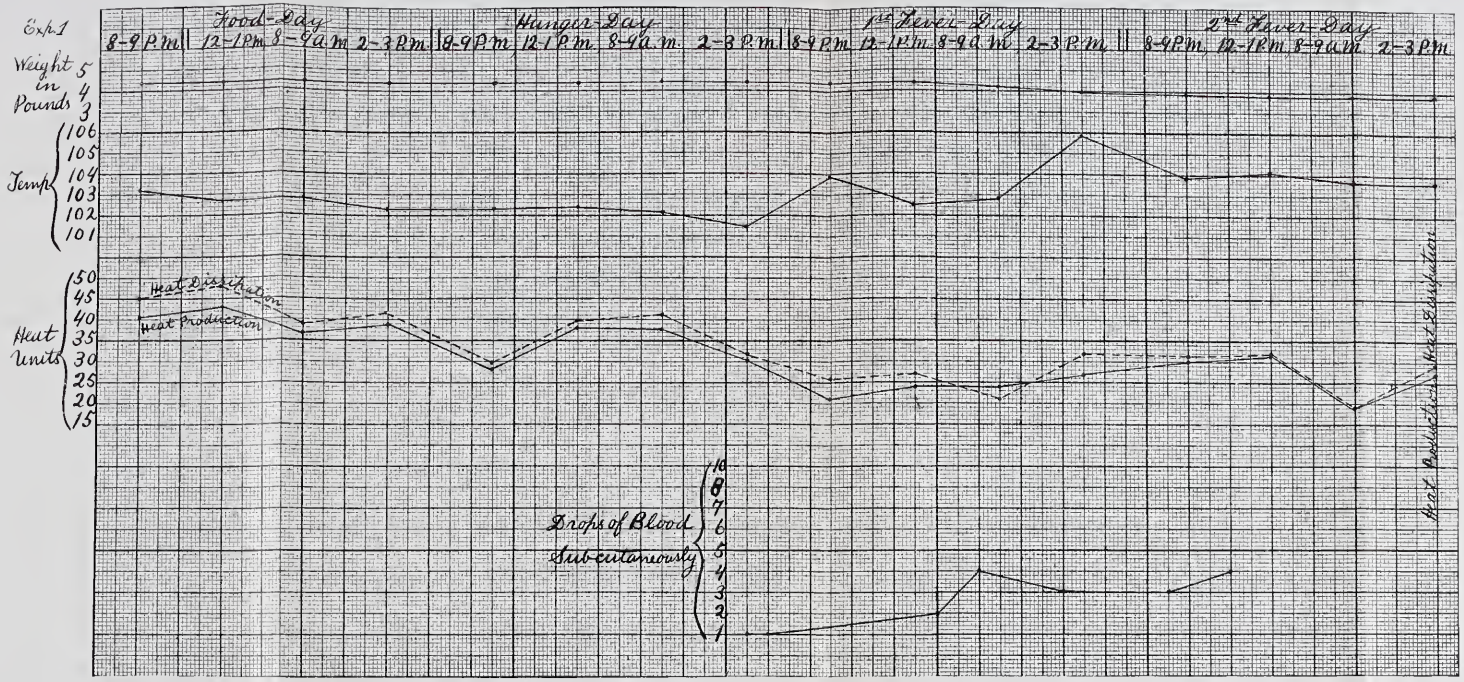
Exp. 1
Food-Day
Hunger-Day
1st Fever Day
2nd Fever Day
8-9 P.M. 12-1 P.M. 8-9 A.M. 2-3 P.M.
Weight in Pounds
Temp
Heat Units
Heat Dissipation
Heat Production
Drops of Blood Subcutaneously
Heat Production Heat Dissipation

Fig. 1.

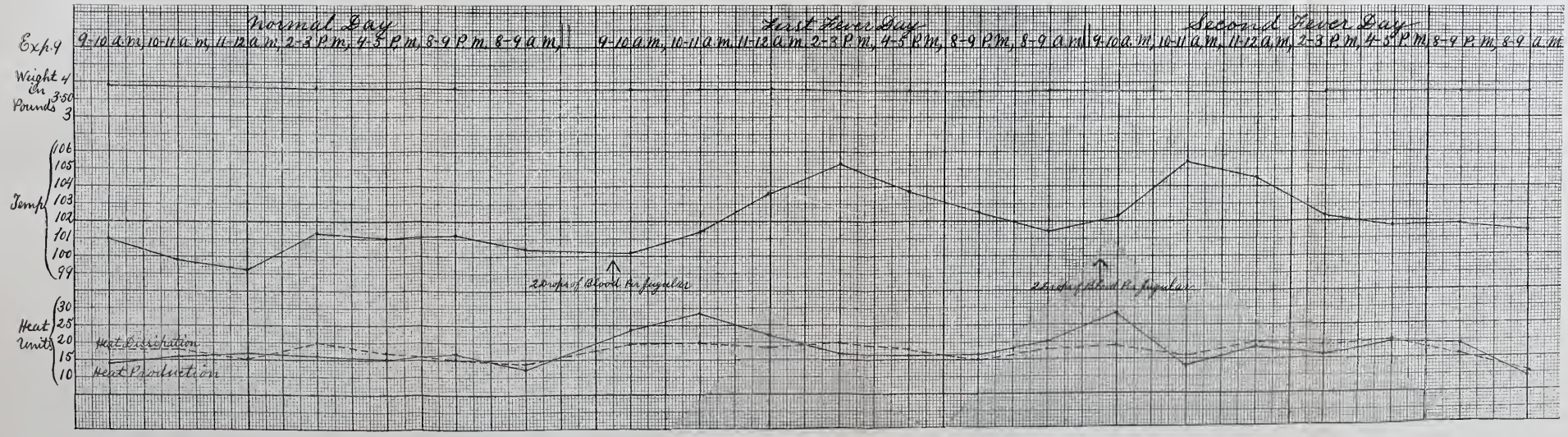
Exp. 9
Normal Day
First Fever Day
Second Fever Day
9-10 A.M. 10-11 A.M. 11-12 A.M. 2-3 P.M. 4-5 P.M. 8-9 P.M. 8-9 A.M.
Weight in Pounds
Temp
20 drops of Blood Per Jugular
Heat Units
Heat Dissipation
Heat Production

Fig. 1.

through the whole apparatus by means of a hose, R, connecting it with the lead tube at B. The space between the cylinders is filled with about four hundred and eighty-four pounds of water. This water is kept thoroughly mixed by means of the agitator O, which has two arms. These arms are pushing the water back and forth thirty times a minute, the motion being caused by water running the motor X, which, by means of the wheel Z and the eccentric, drives the agitator. The thermometer A gives the temperature of the water, and on account of the thorough mixing of the water by the agitator, gives the accurate record of the temperature of the water throughout the apparatus. The thermometer is pushed farther down than is represented in the figure; it usually lies aside of the tube H. The air-tube B, also, has a thermometer to denote the temperature of the air as it is heated up by the man. The thermometer at B is graduated into tenths, while the thermometer at A is graduated into fiftieths, but they are so far apart that one one-hundredth of a degree Fahrenheit can be read. The temperature of the mouth was taken by a thermometer giving tenths. The rectal temperature would have been preferable on account of accuracy. The bucket I receives the water from the motor X, and so conveys it to the water-wheel N, that it runs the meter as an aspirator. The meter is filled with water, and belongs to Voit's little respiration apparatus. The quantity of air aspirated per hour is five to six thousand litres, which is sufficient for respiratory purposes. The instrument is made air-tight by means of the door K, which is clamped by eight powerful iron clamps. The inner edge of the door is lined with rubber. The whole apparatus is enclosed in over six inches of sawdust, the door K having against it a sawdust mattress. The interior of the instrument is lighted by an electric light of one-candle power, by which a paper can be read.

With these arrangements, excepting light, and a mattress inside the instrument, I have tested the apparatus. As the apparatus necessary for the hydrogen test was not available, I used absolute alcohol. The different physicists who have burned a gramme of alcohol have obtained the following various numbers: Thus Rumford obtained 6,195; DuLong, 6,962; Andrews, 6,850; and Favre and Silbermann, 7,183.6. These numbers mean so many gramme-calories, and the number 7,183 is supposed to be the most accurate. In their experiments, in order to allow for the loss of heat due to radiation, a preliminary experiment was made with the body whose heat was sought, the only object of which was to ascertain approxi-

mately the increase of temperature of the cooling water. If this increase be 10°, for example, the temperature of the water calorimeter was reduced one-half this number—that is to say 5° below the temperature of the atmosphere. By this method the water of the calorimeter receives as much heat from the atmosphere during the first part of the experiment as it loses by radiation during the second part. This procedure is called Rumford's compensation. In the human calorimeter the air-tube must be of considerable size for the air to enter, and necessarily permits of considerable loss of heat by the air constantly traversing the instrument. I have tested my calorimeter before and after the performance of the experiments. I give here a test with alcohol:

Time.	A. T.	C. T.	E. T.	Meter.
1.24	83°	74.20°	75.5°	758,274
2.24	82.3°	74.61°	75.8°	762,650
	82.6°	.41°	75.6°	3,376

577.42 = number of heat units required to raise the calorimeter 1° F.

577.42 × .41 rise in calorimeter temperature = 236.74 heat units.

Alcohol burned = 9.235 grammes × 7,183 number of gramme-calories by burning a gramme of alcohol=66.33 kilo-calories. As one kilo-calorie is equal to 3.96 heat units, then 66.33 × 3.96 = 262.66.

V = 3,376 litres of air pumped through the calorimeter.

t = 75.6° — 32° = 43.6 number of degrees the air is heated above 32°.

V + (v × 43.6 × .002035, coefficient of expansion) = 3,376.

V + .0887260V = 3,376.

1.0887260V = 3,376.

V = 3,376 ÷ 1.088 = 3102,9.

W = V × .00285, weight of litre of air at 32° F.

W = 3102,9 × .00285 = 8·84 lbs.

Q = W × t × specific heat.

Q = 8.843 × 7° × .2374 specific heat of air = 14.69, number of heat units given to the calorimeter by the air.

Then 236.74 — 14.69 = 222.05, number of heat units obtained in burning the alcohol.

But the alcohol burned produced 262.77 heat units, and of these 222.05 have been recovered; then 262.66 — 222.05 = 40.61 = loss of heat units or error of the calorimeter. Then the percentage of

error is $40.61 \div 262 = 15.5$. In other words, all results by the calorimeter must have 15.5 per cent. added to them, that they may be accurate. In this paper I have made the percentage of error 16 per cent., as the mean of several experiments showed this to be the average error of the instrument. The constancy of the error made the apparatus one of precision for scientific work.

In my experiments upon man the calculation was made in the same manner. The specific heat of the body was taken to be 0.83.

In estimating the moisture, I used Voit's little respiration apparatus, taking the moisture of the air of the room and deducting it from the moisture of the air coming from the calorimeter. Now, according to Helmholtz, 1,000 grammes of water require 582 calories in evaporation from the lungs and skin; then one gramme of water from the lungs requires $\frac{2301}{1000}$ calories $= 2.304$ heat units to vaporize it.

The glass bulbs were filled partly with sulphuric acid, and weighed upon a delicate balance before and after the absorption of moisture from the air.

By placing a pulley outside the calorimeter and attaching to a leather rope a fourteen pound weight, the man within the instrument was able to exercise. The leather band entered one of the air holes of the instrument. In this manner it was found out: (1) That a man weighing one hundred and ninety-two pounds, during the afternoon produced 410 heat units per hour on an average and not 512 as calculated by oxidation changes and the amount of egesta. (2) Of the whole amount of heat dissipated, about 14 per cent. is thrown off by the lungs. (3) The elevation of about five tons an hour a foot high doubles the hourly heat production.

The study of the calorimetry of malarial fever has never been attempted, except by a study of the changes in the leg or arm. Langlois attempted by an air calorimeter to study the heat production in pneumonia of children, but the instrument is by its construction so inaccurate that it will give only very gross changes.

The instrument used in the study of the malarial paroxysm is accurate in its workings, as has been already detailed. Through the great kindness of Dr. J. F. Berg, of Plainfield, N. J., I was able to study the first accurate calorimetry of malarial paroxysms. Mr. S——— was 5 feet 9½ inches in height, aged 29, a farmer, and the chill he had was the fourth one. During the course of this tertian intermittent fever he was taking no medicine. He ate a very light breakfast at 7.30 A.M. At 8 A.M. his temperature was 98, at

9 30 A.M., 99.2, felt catching pains in the nape of the neck; at 10.18 A.M. he entered the calorimeter, temperature 100.1. While in the calorimeter he had chills running up and down his back, his hands felt cold, and he had a general sense of chilliness. Upon leaving the instrument, 11.18 A.M., his pulse was 84, temperature 101.85; 10.35 A.M., thirsty, feels badly, looks pale, bones and head ache, has a pinched and anxious look; pulse, 92. At 11.47 A.M., again entered the calorimeter, temperature 101.4, left the instrument at 12.48 P.M., temperature 102.0; pulse, 112; complains of heat while in instrument, face flushed, hands moist. At 1.15 P.M. ate a fair dinner. At 1.40 P.M., pulse 84; temperature 100.6; headache, face flushed, some perspiration. 2 P.M., temperature 100.2, entered calorimeter; 3 P.M., left it, pulse 84; inside of calorimeter moist from perspiration; he noted the musty odor for the first time in the instrument. 8 P.M., temperature 98.2; feels quite good; had four movements of bowels, supposed to be due to water not accustomed to.

Second day.—7.30 A.M., ate a good breakfast; entered calorimeter at 9.53 A.M., temperature 99.0; left instrument at 10.53 A.M., temperature $99\frac{2}{5}$; pulse, 84; at 11.22 A.M. entered calorimeter, temperature 99.25. At 12.22 P.M. left it, temperature 99.25; had another movement of bowels, whiskey before dinner at 1 P.M.

At 1.35 P.M. again entered the calorimeter, temperature 99.2; left it at 2.35 P.M., temperature 99.7; pulse, 92; felt well, and left for home on Saturday.

On following Sunday had a light chill. No chills since. One week since the last chill he again entered the calorimeter for a test of his normal heat production. He was well and ate heartily. On the previous day he was engaged in very laborious work.

By means of the electric light (which gives a very uniform heat) of one candle power, he was able to read the morning news while his heat production was being taken. It was found by burning absolute alcohol that, with the electric light, the error was 2.8 per cent. which was deducted from the amount of heat production registered by the calorimeter.

From a study of Fig. 3 it is found that during the initial stage or chill-period of a malarial paroxysm, the dissipation is not as great as at other times, and the heat production is enormously increased. After the fever reached its height, the previous great rise of heat production was succeeded by a great fall, according to the law of compensation. Here high temperature is not an index to a correspondingly high production of heat.

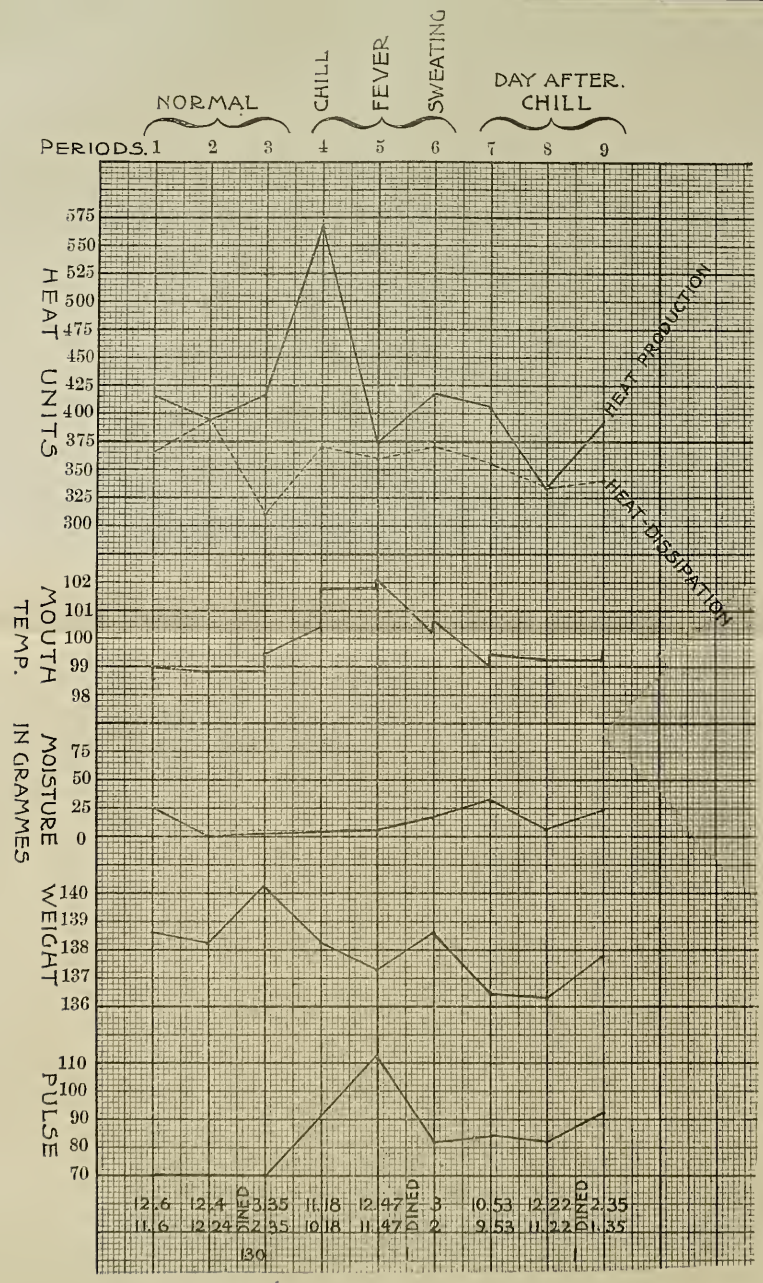
NORMAL
CHILL
FEVER
SWEATING
DAY AFTER. CHILL
PERIODS. 1 2 3 4 5 6 7 8 9
HEAT UNITS
575 550 525 500 475 450 425 400 375 350 325 300
HEAT PRODUCTION
HEAT-DISSIPATION
MOUTH TEMP. IN GRAMMES
102 101 100 99 98
MOISTURE
75 50 25 0
WEIGHT
140 139 138 137 136
PULSE
110 100 90 80 70
12.6 12.4 DINED 3.35 11.18 12.47 DINED 3 10.53 12.22 DINED 2.35
11.6 12.24 2.35 10.18 11.47 2 9.53 11.22 1.35
130

Fig. 3.

In the stage of defervescence, heat dissipation is greatly increased, and heat production does not regain its original height. It is only during the sweating stage that the excess of moisture comes over in the sulphuric acid bulbs on the fever day. If the heat production on the chill day and on the succeeding day is compared with that of the normal day, it will be found to be on the chill day 79.3 heat units in excess, and on the succeeding day 9.6 heat units in deficit. This is a much greater increase than seen in the septic fever of animals.

These observations show how fever in man is originated; that is, usually heat production runs rapidly ahead of heat dissipation, which is partly lessened, and the temperature is elevated. On the next day after the malarial paroxysm there was a slight fever, and the heat production on the average was lower than on the preceding day.

There is every reason to believe that in a continued fever this increase of heat production does not usually last many days, but that the fever continues because of an alteration between heat production and heat dissipation, without regard to an increased or diminished heat production.

My experimental researches lead me to believe that fever is due to an agent from within or without, which deranges the harmony of the thermotaxic, thermogenetic and thermolytic apparatuses, by which in the initial stage the metabolism of the tissues is usually temporarily increased, and this increment is usually greater than that generated upon a restricted amount of nutriment. It is highly probable that, during the chill, heat dissipation is temporarily diminished, but it usually follows the fluctuations of heat production. The four basal thermotaxic centres play the most important part in the temperature-phenomena of fever. That neither increased production nor diminished dissipation is necessary to constitute fever is shown where heat production is diminished, although the temperature is elevated.

High temperature does not cause gravity in fever, for in nervous disorders and in relapsing fever we have high temperatures, 106° F., and no serious symptoms are present. High temperature is an indication of danger in specific fever, not the cause of it. But temperature is only a part of a specific fever; there are many other morbid processes going on, the essence of which has not been grasped. Sir William Jenner puts the facts tersely when he states: "There can be no doubt that the necessity for a healthy condition of the

blood is as essential to the formation of normal secretions as a healthy state of the nervous system. But while we think there is strong evidence in favor of the primary affection of the blood and of the widespread and fearfully severe influence on the system generally of the very deep lesion which in many cases we can demonstrate the blood to have experienced independently of mere admixture of excess of excrementitious matters, we by no means exclude the nervous system or any other part of the body from a share in the production of the symptoms of fever."

It has been observed (very rarely I think) that in meningitis, peritonitis, and certain cases of typhoid fever, the temperature is normal or subnormal. I have shown that in the cortex of lower animals are localized thermotaxic centres, the cruciate and Sylvian, whose function it is to act in harmony with the basal thermotaxic centres to regulate the temperature of the body. In a recent paper I have also shown that in man there are very good reasons to believe in the localization of cortical thermotaxic centres. Now in meningitis the inflammation of the membranes by contiguity may so disorder the thermotaxic centres of the cortex that the temperature may become subnormal, instead of being above normal by an alteration of the harmony between the heat production and heat dissipation. In lower animals it is well known that peritoneal irritation as well as in man greatly reduces the force and frequency of the heart by reflexly stimulating the cardio-inhibitory apparatus and thus keeping metabolism at a low point in the primary stage of a peritonitis. In the case of subnormal temperature of typhoid patients it is easy to see that the disorder of the thermotaxic centres may be such that the relation of heat productiom to heat dissipation is so arranged that the temperature becomes subnormal. An antipyretic usually temporarily produces this state of affairs in normal state. That acute observer, Dr. W. Hale White, has propounded a theory that the cause of fever in certain cases acts upon the nervous centres not directly, but indirectly through the nerves. He states that the rise of temperature noted in fever which is symptomatic of local inflammation bears no relation to the extent of the inflammatory disturbance, and that the tension of the neighboring tissues plays a more important part in the production of fever than does the amount of inflammation. It is certainly the case, he states, that in abscess the temperature as a rule is highest where there is pain and pain in abscess means tension. Dr. White believes that the "calorific centres" of the brain are affected reflexly by the tension

of the inflamed parts acting as a stimulant. He believes that the thermotaxic (which he locates in the cortex), the thermogenetic and thermolytic centres can be acted upon in a reflex manner. In cases of atropia poisoning in lower animals I have seen peripheral irritation cause a rise of temperature. Experiments related further on show how the peripheral terminations of the sensory nerves influence a thermolytic centre, hence it is readily inferred that other thermotaxic centres partly stand in a reflex relation to fever poisons and changes of external temperature. The thermotaxic centres must be mainly reflex in their activity. Hence important factors in heat regulation are the peripheral terminations of the sensory nerves in the skin.*

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* This subject is more fully elaborated in "Fever, Thermotaxis and Calorimetry of Malarial Fever." E. D. Vogel, Easton, Pa.

CHEMISTRY.

In the search by chemists to produce quinine by synthesis, modern chemistry has put us into the possession of a series of organic bodies which have the power to reduce the temperature of the body. The four bodies pyridin, quinolin, kairin and thallin have, in a chemical sense, a very close genetic relationship.

Pyridin is a part of Dippel's animal oil, itself a product of dry distillation of protein substances: the relation of pyridin to quinolin is shown by the fact that quinolin can be converted into the former. When quinolin is oxydized by permanganate of potash, there is obtained a bibasic quinolinic acid $C_5H_3N(COOH)_2$, whose lime salt $C_5H_3N(COO)_2Ca$, mixed with an excess of lime and then distilled in the dry way, produces pyridin. The chemical metamorphosis is as follows: $C_5H_3N(COO)_2Ca+Ca(OH)_2=C_5H_5N+2CaCO_3$. It has been known for a long time that quinolin has been found in Dippel's oil and coal tar. Especially interesting here is a formation of quinolin by heating the alkaloids of Peruvian bark with potash. From pyridin and quinolin are obtained bodies of a phenol nature like the phenols from benzol and naphthalin.* We are interested in only two phenols of oxyquinolin—$C_6H_3(OH)C_3H_3N$—that is, in ortho-oxyquinolin and paroxyquinolin, two isomeric bodies which contain the hydroxyl (OH) in the "benzol nucleus" of the quinolin molecule, but the same elements have a different arrangement. The ortho-oxyquinolin is a mother substance of kairin and paroxyquinolin, or rather its methylæther (also tetrahydro-paraquinanisol) $C_9H_{10}(OCH_3)N$, a body discovered by Skraup, and called thallin. These antipyretics are phenol compounds, and the first one I shall speak of is kairin. Methyl karin $C_6H_4[(CH_2)_3NCH_3]HCL$ is the salt known as kairin M., and the ethyl salt as kairin A. Kairin A. is generally employed in medicine, and is a grayish powder of slight phenol-like odor, of a saline, bitter and somewhat aromatic taste. It is with difficulty soluble in cold water, more soluble in hot water, with difficulty

* Biach. Die Neuern Antipyretica, 1889.

soluble in alcohol and glycerine, and nearly insoluble in ether, chloroform and carbon bisulphide; it melts at 110° C.

Hydroquinone $C_6H_4(OH)_2$ forms colorless prisms soluble in seventeen parts of water at 15° C., more readily soluble in alcohol and ether. It melts at 169° C. It is changed into quinone by the action of oxydizing agents.

Antipyrin was produced by Knorr by synthesis and introduced into practice by Filehne, of Erlangen. It is obtained by the action of acet-acetic ester upon methyl-phenyl-hydrazin. Repeated experiments by Knorr have shown that it is phenyl-dimethyl-pyrazolon $C_6H_5)N\begin{matrix}CO—CH\\ N(CH_3)\text{-}C\text{-}CH_3\end{matrix}$. It is a white crystalline powder in scales, and is very soluble in water. It melts at 113° C. Its most characteristic reactions are with ferric chloride, with which it turns dark red, and with nitrous acid or nitrites, with which it turns emerald green, forming isonitroso-antipyrin $C_{11}H_{11}N_3O_2$.

Thallin—tetrahydro quinanisol $C_9H_{10}N\ (OCH_3)$. It crystallizes in rhombic crystals, fusing at 40° C., of a peculiar, pleasant, aromatic odor, soluble in ether, alcohol and water. The salts that are used are the tartrate, tannate and sulphate. The latter, now known as commercial thallin, is a white crystalline powder which fuses at 110° C, and is moderately soluble in water, but with difficulty in cold alcohol. A drop of ferric chloride solution produces a beautiful dark green color which, in the course of a day, becomes red and ultimately yellow. The reaction will show in extremely dilute solutions. The name is due to this reaction, which is produced by a variety of oxydizing agents.

Acetanilide under the name of antifebrin. Cahn and Hepp, in 1886, put it forth as an antipyretic; it is a substitution product of aniline $C_6H_5NH_2$; and if an atom of hydrogen of the amido group is replaced by acetic acid, then antifebrin is obtained. Antifebrin $C_6H_5NHC_2H_3O$ exists in white crystalline scales or needles, according to the solvent from which it is recrystallized, melting at 120° C. and boiling at 292° C. and sublimable; it is odorless, tasteless, with difficulty soluble in cold water (1 in 60), and in hot water 1 in 50, easily soluble in ether, chloroform and benzol.

Acetphenetidin—oxyethylated antifebrin is the ethyl combination, and its formula is $C_6H_4(OC_2H_5)NHC_2H_3O$. Phenacetin in composition is analogous to antifebrin, and forms a white crystalline powder, perfectly tasteless and odorless, melting at 135° C., slightly soluble in water, hot or cold, somewhat more so in glycerine, but freely soluble in alcohol and ether.

Antithermin, phenyl-hydrazin-levulinic acid $C_6H_5N_2HC\text{-}(CH_3)\text{-}CH_2COOH$, is prepared by dissolving phenyl-hydrazin in dilute acetic acid and then adding a solution of levulinic acid. This causes a yellow precipitate to form, which crystallizes from alcohol in well-formed prismatic crystals.

Pyrodin $C_6H_5N_2H_2(C_2H_3O.)$. The formula of acetyl-phenyl-hydrazin shows a marked relation to antifebrin $C_6H_5NHCH_3CO$, differing from it but by the increment of one sole imido group (NH); its derivative composition from phenyl-hydrazin with an acetic acid residue relates it likewise to antithermin $C_6H_5NHN\text{-}(CH_3)C(CH_2CH_2COOH)$, which is produced by the dehydration of a combination of phenyl-hydrazin with levulinic acid (Beta-aceto-propionic) a higher homologue of acet-acetic acid. Equally the derivation of antipyrin $C_3H(CH_3)_2N_2(C_6H_5)O$ from a phenyl-hydrazin compound with acet-acetic-acid ester places this substance in relation with pyrodin, and the analogy between antifebrin and its kin, phenacetin $C_6H_4(OC_2H_5)NHCH_3CO$, differing by the substitution of an oxyethyl group (OC_2H_5) for a hydrogen atom, brings the latter antipyretic phenacetin into the line of chemically and therapeutically related compounds. It is a white crystalline powder, very sparingly soluble in cold water.

Exalgin, properly methyl-phenyl-acetamide, or methylated antifebrin $C_6H_5NCH_3C_2H_3O$, is a direct derivative of antifebrin, formed by the substitution of a methyl group for a hydrogen atom in the original phenyl-acetamide. It was discovered by Briggonet, of Lyons, of the Cochin Hospital. It occurs in needles or in large white tablets, according as it is obtained by crystallization, or from the mass after distillation. It is slightly soluble in cold water, more soluble in hot water, and very soluble in cold water containing a little alcohol.

Thermifugin is methyl-trihydro-oxyquinolin, carbonate of sodium $C_9H_8(CH_3)NCOONa$. This acid was discovered by Nencki, of Basel. Its sodium salt has been found by Dr. Demme, of Berne, to be an interesting antipyretic. It is said to combine the three effects, of reducing temperature, of retarding pulse, and of increasing blood-pressure. The free acid forms beautiful crystals which are but little soluble in water or alcohol and melt at 265° C. The sodium salt is faintly yellowish white, lustrous, and dissolves to form a brown solution. Methacetin is oxymethylated antifebrin, or acet-para-anisidin, is similar to phenacetin, and is derived from amido-phenol. The relation of these compounds with antifebrin is hown by the following formula :

$C_6H_4\langle{}^{H}_{NH}\rangle(CH_3CO)$ Antifebrin.

$C_6H_4\langle{}^{OC_2H_5}_{NH}\rangle(CH_3CO)$ Phenacetin.

$C_6H_4\langle{}^{OCH_3}_{NH}\rangle(CH_3CO)$ Methacetin.

It is a slightly reddish powder of saltish bitter taste and without odor. The powder is composed of fine crystalline scales, which melt at a temperature of 127° C. It is soluble in cold water, more so in warm water, and still more so in alcohol.

Antisepsin $C_6H_4BrNHC_2H_3O$, or para-mon-brom-pheyl-acetamide, or bromated antifebrin, is the latest. Here bromine is introduced by substitution for a hydrogen atom in antifebrin. It is devoid of odor and taste. It crystallizes in small pearly prisms, melting at 328° F. It is insoluble in cold water, with difficulty soluble in hot water, only slightly soluble in glycerine, and easily soluble in alcohol and ether.

Other Antipyretics.

Through the great kindness of Professor E. Hart, of Lafayette College, I have been furnished with some new antipyretics. Thus,

Paranitro-acetanilide $C_6H_4{}^{NHC_2H_3O}$

Sulphanilic acid $C_6H_4\langle{}^{NH_2}_{SO_2OH}$

and

Sulphanilate of soda $C_6H_4\langle{}^{NH_2}_{SO_2ONa}$

have the power to reduce the temperature in the lower animals. In man sulphanilic acid (3 grains) relieved a headache.

Sulphanilate of soda kills the lower animals by diastolic cardiac arrest, when given in doses of thirty grains per jugular. When ten grains of it were given to a man, no appreciable effect was observed, although the pulse seemed a little weaker. Of the above antipyretics the only one soluble in water is sulphanilate of soda.

PHYSIOLOGICAL AND PATHOLOGICAL ACTION.

HOW DO ANTIPYRETICS ACT?

There are two views about the action of the antipyretics—one that they influence metabolism by an action upon the nervous system, the other that they directly act upon the thermogenic tissues. The researches upon the nervous system seem to indicate six centres which have a thermotaxic function. Thus two in the cortex, the cruciate and Sylvian, and at the base of the brain four, as is illustrated in Fig. 4—one beneath the corpus striatum in the gray matter 1, a second about the nodus cursorius of the corpus striatum 2, a third in the gray matter at the anterior inner end of the optic thalamus 3, and a fourth in the gray matter about the most anterior end of the 3d ventricle 4. The fourth basal thermotaxic centre is also the thermopolypnœic centre and a thermolytic centre. It is common knowledge that when an animal is exposed to a heated atmosphere it breathes very rapidly. I have discovered that this is due to the thermopolypnœic centre, for if this centre is destroyed the frequency of the respirations is arrested. That this is really due to thermic irritations conveyed by nerves to the polypnœic centre was proved by experiments which I have made. If the cortex cerebri of a rabbit is removed under ether, and a test-tube filled with hot water applied to the thermopolypnœic centre in the brain itself, then the number of respirations is increased, provided the external temperature is sufficiently high to start polypnœa. Here the heat increased the irritability of the polypnœic centre. When polypnœa is started a piece of ice applied to the polypnœic centre reduces the frequency of the respirations. The heat is not able to excite rapid respiration through central stimulation, for it can act only through the peripheral terminations of the sensory nerves upon the centre.

Here the stimulation of the peripheral endings of the sensory nerves by heat excites this centre, and it sends out in a reflex manner impulses to the respiratory centre, and thus excites it to increased activity, that more heat may be dissipated through the watery

vapor thrown off by the lungs. I have made some experiments to determine whether the antipyretics act upon this thermotaxic centre. To do this, the animal, a rabbit, was etherized, a T canula inserted into the trachea, and a curve taken by means of Marey's polygraph. Then the animal was placed in a chamber which was partly closed and had a temperature of about 100° F., and curves taken occasionally till the rectal temperature reached 106–107°, then the antipyretic was given, and the animal permitted to cool down, when he was again heated up to 106–107° F., and the number of respirations noted. It was first found that reheating, as a rule, increased the number of the respirations, whilst the antipyretics usually reduced it. The results obtained were as follows: with kairin, doses of 2–5 grains per stomach caused a diminution of

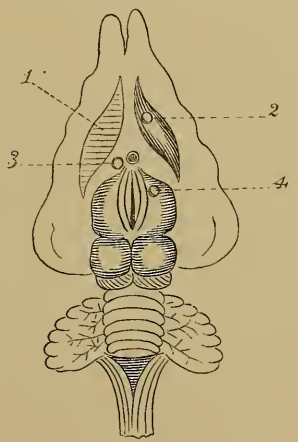

Fig 4.

polypnœa. With thallin a diminution also ensued, and with antifebrin a similar result. When phenacetin was given by the stomach, the second heating increased the polypnœa, but when it was given by the jugular it decreased the polypnœa. The administration by the stomach did not affect the polypnœa, because of the drug's insolubility. Antithermin also lessened polypnœa. Pyrodin in full doses lessened polypnœa. Exalgin also diminished polypnœa, but this was probably due to the dyspnœa caused by the convulsive movements. Hydrochinon by the jugular lessens polypnœa, by the stomach or hypodermically it has but little effect. Quinine also diminishes polypnœa, either with or without the presence of the cortex cerebri. The question now arises, how is this retardation of polypnœa by

antithermics brought about? Is it due to a lessened irritability of the sensory nerves, the thermopolypnœic centre, the respiratory centre or the respiratory neuro-muscular apparatus? Whilst for each individual antipyretic I am unable to exclude an action upon the respiratory centre, yet the doses of bisulphate of quinine absorbed when given subcutaneously are not able to depress the centre of respiration, but rather to stimulate it. It does not depress the sensory motor nerves or muscular irritability. Hence by exclusion the action must be upon the polypnœic centre. This result makes it a reasonable conclusion that the other antithermics partly act upon the polypnœic centre, reducing its activity. But this is a thermotaxic centre; hence it is a natural inference that the antithermics change the temperature by an action upon the thermotaxic centres, and through them upon the tissues.

Further proof that the antithermics act through the thermotaxic centres upon the metabolism of the tissues is obtained by the experiment of dividing by a transverse section the brain just back of the corpus striatum, and then giving antipyrin by the jugular. Here no fall of temperature ensued as happened previous to the section. The fact that antipyretics have but little action upon man in health, and a marked one in fever, is a strong argument for their action upon nerve centres which are known to be disordered by the poison of fever. The chain of action between these thermotaxic centres and the tissues is not absolutely made out; if it is a direct one, it is through ganglia in the spinal cord which are supposed to be thermogenic centres.

One of my students, Dr. P. J. Martin, found that striate hyperthermia produced by puncture was depressed by several of the modern antithermics. The heat production was also lessened. These experiments have been confirmed by Girard and Gottlieb. Girard has also shown that if an animal is under antipyrin, puncture into the striate body does not cause as great a rise as formerly. Gottlieb believes antipyrin and quinine to act differently in reducing temperature. Antipyrin reduces striate hyperthermia by a sedative action upon the nerve centres; and when the animal is antipyrinized and exposed to a high temperature, heat regulation is so disturbed that the temperature rises, although the control-animal experiences hardly any rise. In striate hyperthermia, quinine exerts only a small influence in reducing it, and a high external heat does not affect the thermic regulatory apparatus like antipyrin, for the temperature does not rise. It is difficult to understand why quinine

does not act upon metabolism in health as it does in fever if it has a direct action on tissue-metamorphosis. Possibly in Gottlieb's experiments it was not absorbed to any great extent.

Now, as to the action of the antipyretics upon tissues—if they acted directly, they would act in health as in fever upon the blood. In large doses they cause changes in the hæmoglobin, but the same results ensue with doses where no changes in the blood are discoverable. They also interfere with the oxygenation of the blood, but for reasons above mentioned this would not suffice to explain their

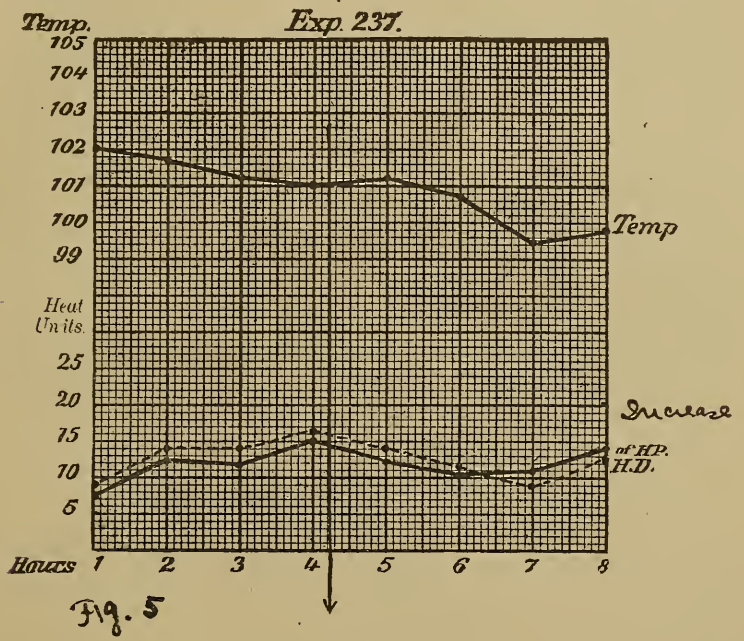

Fig. 5.

action upon temperature. As to nitrogen-elimination, the most careful experimental results are diametrically opposed to each other, some showing an increase, others a decrease. Both statements are probably true, for my calorimetric experiments show that when antipyretics are give to an animal, and the heat production, heat dissipation and temperature are studied for some hours before and after the drug, it is found that the depression of temperature is often accompanied by a temporary decrease of heat production, but this decrement of heat production has no necessary relation to the fall of temperature, for I have often seen the temperature fall (Fig. 5),

and the heat production increase or even the temperature increase and the heat production fall (Fig. 6).

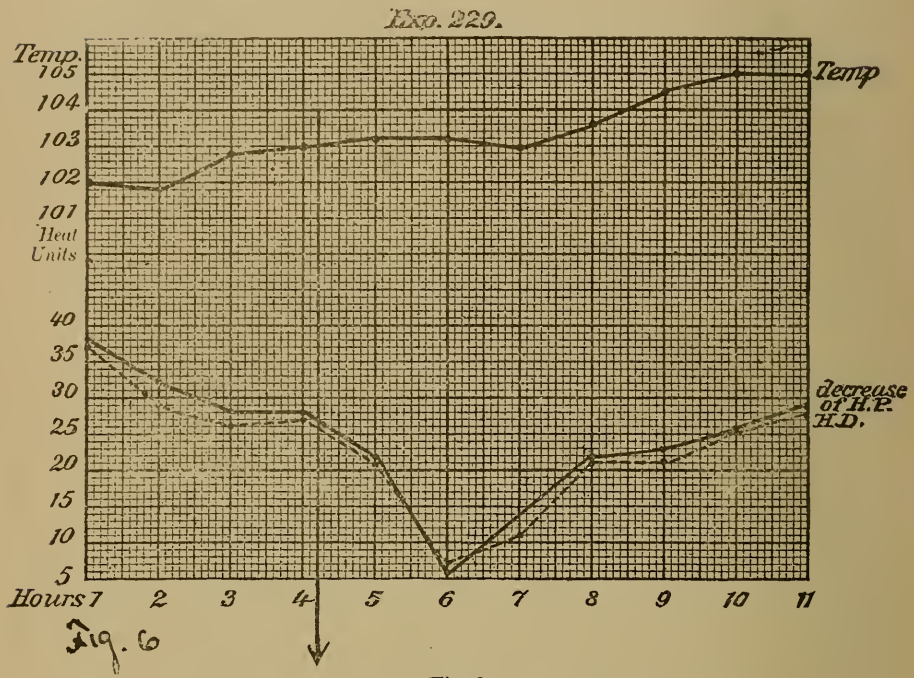

Fig. 6.

THE ACTION OF ANTIPYRETICS IN FEVER.

It is of much interest to pursue the study of medicaments upon man in a state of fever. Whilst experiments upon animals are of great value they must be substantiated by similar observations upon man to make them of import to the physician using them. These experiments were made upon a man weighing 182 pounds, æt. 36, height 5 feet 10 inches, who had a slight fever, due to chronic nephritis, complicated by dropsy and albuminuric retinitis. He ate a large breakfast at 7 A.M. and entered the calorimeter a few hours afterward. Observations were made hourly and with the calorimeter already described. The hour about 11 A.M. was usually taken as the normal hour, so that all subsequent hours under the antipyretic might be compared with it. The patient neither ate nor drank during the day. It was found that taking the time of 11 A.M. was

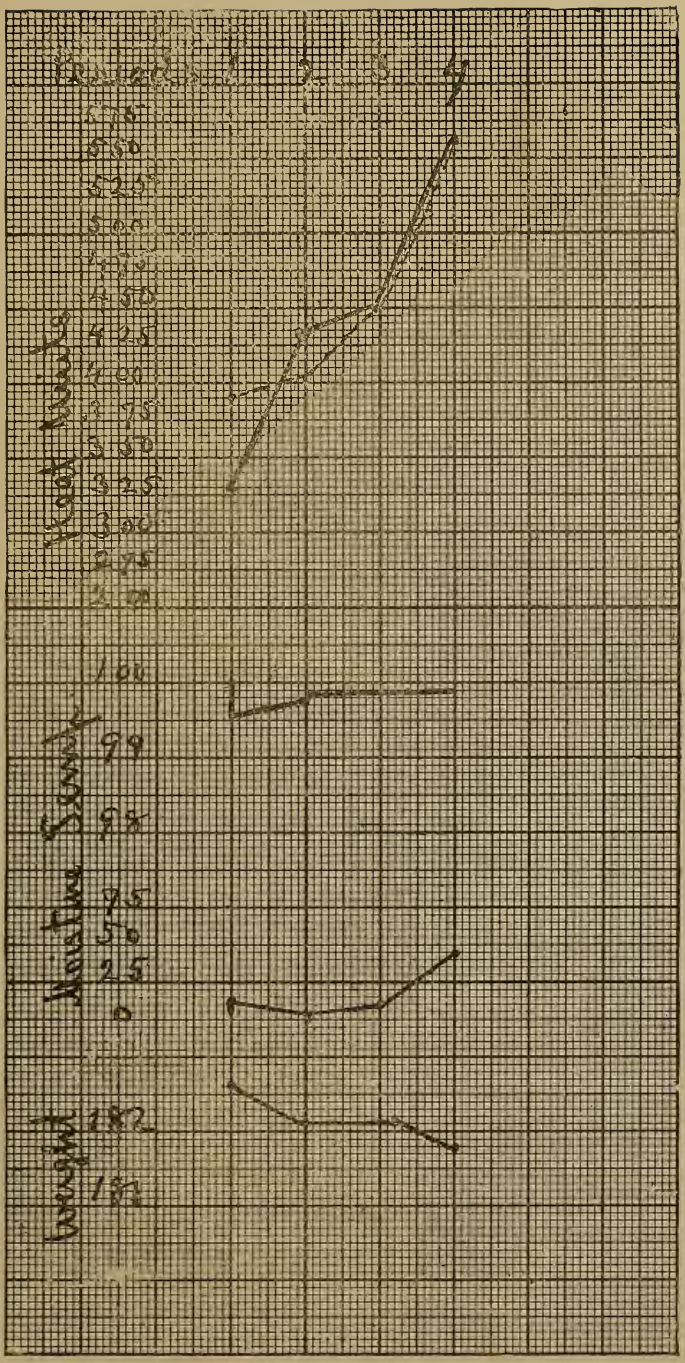

Fig. 7.

fair, for both heat production and heat dissipation rose, as is seen in Fig. 7. Hence any fall of heat production after 11 A.M. must be attributed to the drug and not to natural causes.

The medicine was always given by the mouth.

In Fig. 8 is shown the effect of ten grains of quinine upon the patient. The heat production before the drug was given by the stomach was 510.06 heat units, and heat dissipation 562.59. In the first hour after the drug was given, heat production was 481.86 heat units, and heat dissipation 549.3. In the second hour heat production was 535.5, and heat dissipation 558.8, although the temperature was falling. During the third hour heat production was 453.0, and heat dissipation 460.4. In Fig. 9 is exhibited the effect of twenty grains of antipyrin. Before the drug was given, both heat production and heat dissipation were 411.93 heat units. During the first hour after the drug, heat production was 328.8 heat units, and heat production 404.5. During the second hour, heat production was 450.9, and heat dissipation 436.0 heat units, and during the third hour heat production and heat dissipation were 393.0 heat units. In Fig. 10 are given the curves of heat production and heat dissipation of antifebrin. Before the drug heat production and heat dissipation were 291.8 heat units. After the drug was given, in the first hour heat production rose to 350.3, and heat dissipation to 345.3. During the second hour after the drug, heat production was 344.5 heat units; heat dissipation, 329.4. A second dose of acetanilide was given, and during the third hour after the first dose heat production fell below normal to 230.8 heat units, and heat dissipation to 280.1 heat units. In the fourth hour after the first dose, heat production rose above normal to 334.8 heat units, and heat dissipation to 319.0 heat units. During the fifth hour after the first dose, heat production was 307.7 heat units, heat dissipation 337.6 heat units—still above normal, although the temperature curve had descended to its lowest point. With phenacetin (Fig. 11) before its use heat production was 302.5, heat dissipation 272.8, whilst during the first hours after its use heat production rose to 349.3, and heat dissipation to 334. In the second hour after the drug, another dose of phenacetin having been given, heat production remained at 375.3, and heat dissipation at 405.1. In the third hour after the drug, heat production fell to 248.1, and heat dissipation to 307.3. In the fourth hour after the drug, heat production was 395.2, and heat dissipation 351.2.

If the figures preceding are attentively considered, it will be found that fall of temperature is not necessarily attended by a fall

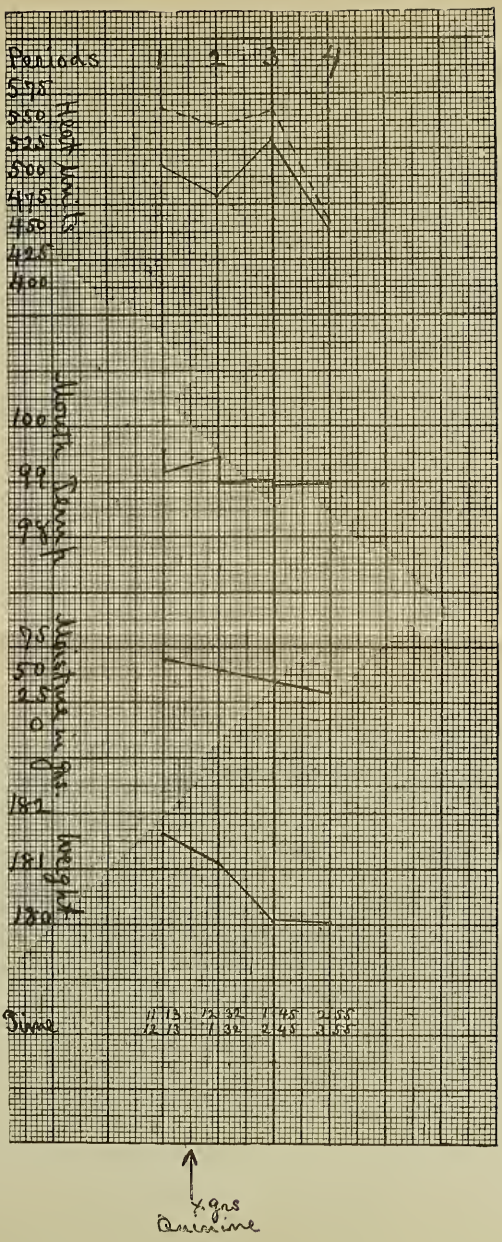
Periods
1
2
3
4
575
550
525
500
475
450
425
400
Height of Mercury
100
99
98
Humidity in Percentages
95
50
25
0
Humidity in Grs.
187
181
180
Weather
June
11 13
12 13
15 32
1 32
1 45
2 45
2 55
3 55
Grs
Ozonine

Fig. 8.

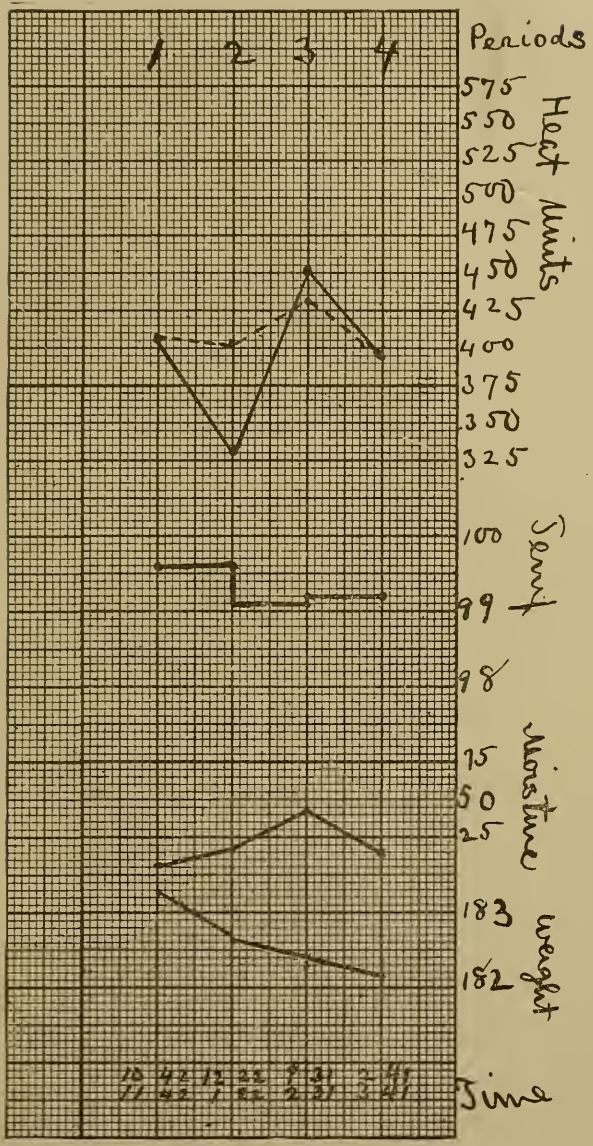
1
2
3
4
Periods
575
550
525
500
475
450
425
400
375
350
325
Heat units
100
99
98
Temp
75
50
25
Moisture
183
182
weight
Time
Antipyrin
20 grs

Fig. 9

Periods
1
2
3
4
5
6
575
550
525
500
475
450
425
400
375
350
325
300
275
250
225
100
99
98
75
50
25
0
182
181
Heat units
Temp
Moisture
Weight
Time
10 39
11 39
11 47
12 47
2 55
1 55
3 4
4 4
3 13
4 13
9 21
10 21
Antifebrin
5 grs
5 grs

Fig. 10

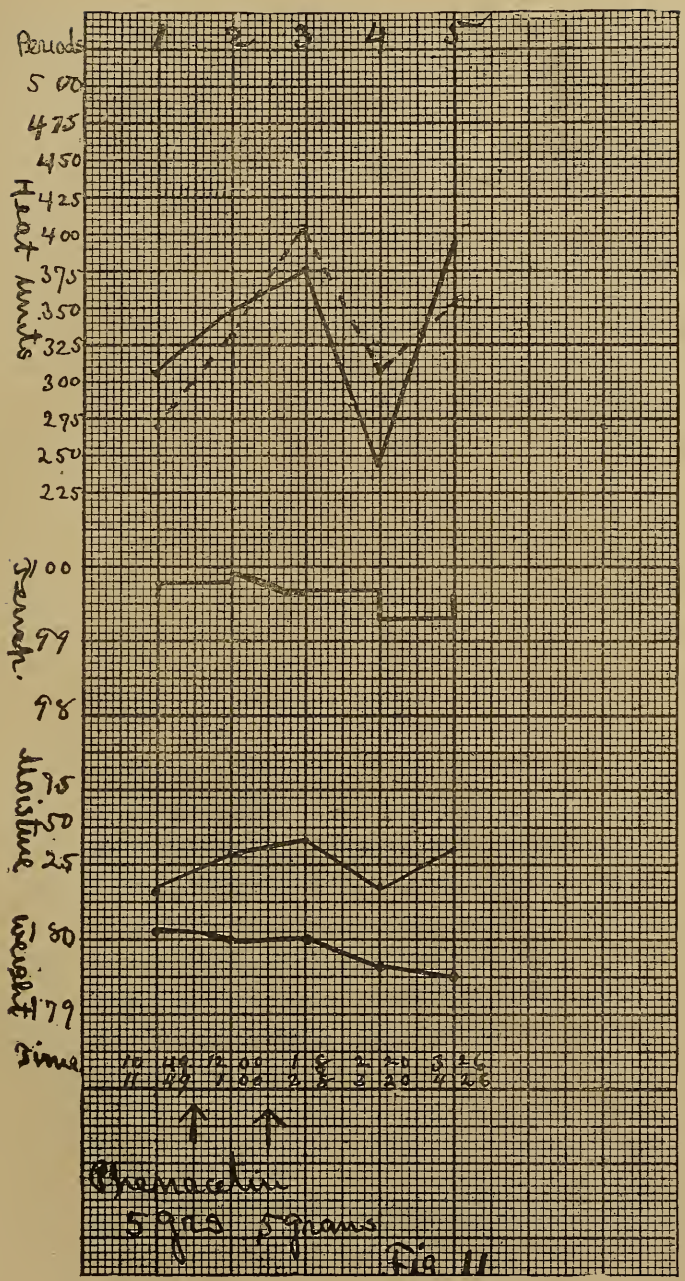
Periods
1
2
3
4
5
Heat units
500
475
450
425
400
375
350
325
300
295
250
225
Temp.
100
99
98
Moisture
75
50
25
Weight
80
79
Time
Quantities
5 grms
5 grms

Fig II

of heat production, for it may be increased. Hence the following conclusion is justifiable. Fever usually is set up by a temporary increase of heat production beyond that of heat dissipation, whilst antipyresis usually is set up by a temporary decrease of heat production beyond that of dissipation. In fever neither a high temperature nor an increased production of heat is a necessary concomitant; but as the temperature mainly depends upon an altered relation of heat production to heat dissipation, so in antipyresis neither a low temperature nor a lessened production is a necessary associate, but the fall of temperature mainly depends upon an altered relation of heat production to heat dissipation.

In the lower animals some of the antipyretics act differently upon heat dissipation than they do upon man.

THERAPEUTICS.

It was necessary to know what the antipyretics were chemically, how they acted physiologically, to determine their general therapeutic activity, their toxicological effects and the differences between them.

I shall take up each one separately and state the diseases in which they have been used. The chemical constitution of the antipyretics is thought to indicate the different activities of these bodies. Thus antiseptic properties predominate in the alcohol hydrate derivatives, as in naphthol, whilst the antithermic properties are most prominent in the amidogen derivatives, as in antifebrin, thallin, kairin. A predominance of analgesic properties exists in the amidogen compounds in which an atom of hydrogen has been substituted by a molecule of a fatty radical, especially of methyl, as in antipyrin, phenacetin and exalgin.

KAIRIN.

Physiological Action.

The blood is not able after its use to take up its usual amount of oxygen. It increases usually the pulse and diminishes the number of respirations. In frogs the respiration is quickly arrested, but death ensues from cardiac paralysis. It causes hyperæmia of the kidney and bloody urine. In large doses in animals, kairin retards the pulse; has but little influence upon arterial tension, and death is due to paralysis of heart, and the blood changes. Maragliano found in man that the blood-pressure rose a little, and the pulse diminished in frequency. Subcutaneously in animals it causes considerable loss of sensibility, with stupor, and myosis.

Small doses increase the amount of carbonic acid thrown off by the lungs, whilst large doses decrease it. In man kairin acts like phenol, and unites with sulphuric acid, being excreted in the urine as such. Part of the kairin in the urine is still furthur oxydized and colors the urine. After large doses of kairin there is found in the urine phenyl-glycuronic acid. Kairin appears in the urine

within a half hour after its administration, and diminishes the urinary nitrogen. In man by its exhibition it causes burning in the nose and eyes, decrease of respiration and increased diaphoresis during the depression of temperature, and a chill at its ascent. Dr. P. J. Martin found in rabbits that heat production was diminished by it in striate hyperthermia produced by puncturing the corpus striatum. The heat dissipation was increased.

Therapeutics.

Owing to its toxicity it has been discarded for safer antipyretics.

HYDROCHINON.

Physiological Action.

According to researches of Dr. P. J. Martin, small doses in frogs produced spinal convulsions, loss of power over extremities, and a want of sensibility due to central causes. It has no action upon the motor nerves. In rabbits it lessens the number of pulsations and the force of the heart. In small and large doses it increases the arterial tension due to an action upon the main vaso-motor centre and the heart. It increases the respiratory frequency, which is caused by a central excitation. It usually (according to Dr Martin) in small doses decreases the heat production and heat dissipation.

Therapeutics.

It is an efficient antipyretic, and its use is apparently unattended by any injurious effects. The antipyretic effect of single doses is comparatively temporary, but in hyperpyrexial conditions a moderate temperature can be safely obtained by repeated doses. A dose of 15 grains produces no cardiac depression, but moderate hydrosis In a case of phthisis I found it quite efficient in controlling the temperature.

THALLIN.

It derives its name from the fact that when chloride of iron is added to it the solution assumes a green color. Subcutaneously in the rabbit it produces convulsions in two hours. In dogs it reduces the arterial tension and the cardiac pulsation. The lessening of blood-pressure is mainly due to an action upon the peripheral vaso-motor apparatus. According to Beyer it accelerates the coagulation of the blood and arrests the heart in cold-blooded animals by

a stimulation of the ends of the vagus. It destroys hæmoglobin. In man it reduces considerably the blood-pressure. In animals the fall of temperature is not proportionate to the dose. It diminishes the urea and exhalation of carbonic acid. It makes the urine dark brown; and chloride of iron, if added to the urine, produces a red color. According to Dr. P. J. Martin, thallin decreases temperature in striate hyperthermia by diminishing heat production and increasing heat dissipation.

Therapeutics.

This drug has been found active in typhoid fever, pneumonia, phthisis, pleurisy, diphtheria, erysipelas and intermittent fever. It is the most powerful in the fever of phthisis, but less powerful in pneumonia and typhoid fever. In nearly all cases, an hour after the first dose the temperature had fallen greatly, and afterward seldom reached its original height. The fall of the temperature is usually very short, and after the end of the third hour gradually rises. Vomiting, collapse and cyanosis are observed. Sweating is nearly always present. The manner of the fall and subsequent rise of temperature is progressive. The chilliness is the most disagreeable accompaniment of this drug. Thallin is absorbed by the stomach and eliminated by the kidneys with excessive rapidity. Hence, unlike the other antipyretics, it must be given in small and repeated doses to have its full effect. Unlike antipyrin, no exanthem resulted from it. According to Ehrlich and Laquer, the results of this drug in typhoid fever are very excellent. In pneumonia it is not to be recommended on account of its depressing action upon the heart.

A contra-indication is valvular disease of the heart and also the different forms of nephritis. In gonorrhœa two per cent. solutions shorten the course of it by ten to eighteen days. The dose is two grains hourly.

ANTIPYRIN.

It is a grayish, crystalline powder of a slightly bitter taste, and is freely soluble in water and alcohol. It causes death in frogs and rabbits by cardiac paralysis. In small doses in the just-mentioned animals it produces an excitation of the brain, medulla oblongata and spinal cord, followed by a paralysis of the same organs. Batten and Bokenham found antipyrin to act upon all parts of the nervous system, mainly on the spinal cord, but also on the brain and motor

nerves, the symptoms in question bearing a strong resemblance to those seen in lateral sclerosis. For instance, in cats spastic rigidity of the hind limbs was found. They think it affects the lateral columns of the spinal cord. From the rapid rhythmic movements, and the circus movements observed in many cases, it may be concluded that either the motor centres themselves are involved or their inhibitory power abolished. It causes tetanic convulsions, and the subsequent paralysis of the nerve centres is followed by a disappearance of reflex excitability. If directly injected into the muscle, it loses its irritability. It decreases the excitability of the sensory centres. When an animal is thrown into convulsions, pinching the feet will arrest them for a while. If antipyrin is first given by the vein, then strychnia does not cause convulsions. The electric irritability of the sciatic nerve during the poisoning was lessened. In warm-blooded animals antipyrin causes an increase of arterial tension with acceleration of heart beat, whilst with large doses the pulse remains the same, the blood-pressure sinking on account of dilatation of the capillary vessels. It has, in ordinary doses, no influence upon the hæmoglobin.

The acceleration of the heart beat is due to a stimulation of the cardio-motor ganglia. This increase of arterial tension is alone due to increase of cardiac activity, and not to vaso-motor activity. The depression of arterial tension is due to diminution of activity of cardiac muscle and the vascular dilatation. It has a hæmostatic action when locally applied, being more powerful than ergotin or iron salts. In man plethysmographic experiments show a dilatation of the capillaries. Its antizymotic action is much smaller than that of the other antipyretics. In small doses it had no effect upon digestion or the secretion of gastric juice. The vomiting it causes is of central origin. It is rapidly eliminated by the kidneys, appearing in the urine in half an hour, and being for the most part eliminated in twelve hours. It causes the urine to be somewhat darker, and often discolors it. In healthy persons it diminishes the urine twenty to forty per cent., and the solid substances sixteen per cent. It increases the amount of sulphuric acid in the urine. The fall of temperature is independent of diaphoresis or of any action upon the general circulation. Drs. Wood, Reichert and Hare found that it reduced heat production and heat dissipation in pepsin fever of animals. Dr. P. J. Martin has shown that antipyrin reduces the hyperthermia generated by puncture of the corpus striatum, and Girard has given the antipyrin first, and shown that puncture of

the striate body does not cause as great an elevation of temperature as it normally does. After section of the spinal cord, antipyrin is powerless to depress temperature, showing that the drug does not directly affect the tissues. The depression of temperature in the interior of the body goes hand in hand with the increase of temperature of the skin. It accelerates the respiration.

Antipyrin, antifebrin and thallin, when fed for days to animals, cause progressive emaciation, prostration, falling out of hair, and development of cutaneous ulcers, ending in death.

Therapeutics.

The action of antipyrin is of varying duration, usually seven to nine hours; and after the depression of temperature, it gradually ascends. The descent of temperature is usually accompanied by hydrosis, and the ascent is without chilliness. The fall of temperature begins about the end of an hour, and reaches its maximum in three to five hours. The pulse and temperature usually fall together, but there is no complete relation between the two. Dr. Drasche has found antipyrin to excite fever repeatedly in a woman, aged 52, afflicted with rheumatism. In pneumonia, typhoid and other fevers, acute rheumatism, erysipelas and tuberculosis, antipyrin is a safe and promptly-acting antipyretic. It is powerless to prevent the return of the chill, although usually well borne.

Dr. Prout believes antipyrin to be a remedy absolutely certain to cut short the duration of a paroxysm of malarial fever, and when used in combination with quinine shortens the whole attack. Where the temperature remains persistently high, there antipyrin possesses the power of producing diaphoresis and diminishing fever. One of the most striking effects when administered during the hot stage is the almost immediate sense of relief. In the intense throbbing headache, the constant feeling of oppression, the aches and pains in the loins and limbs, antipyrin acts as a sedative, the patient becomes drowsy, and, after a second dose, usually falls into a sound refreshing sleep. At the same time the skin begins to feel moist, and this increases till the patient is bathed in perspiration. Quinine intensifies the action of antipyrin as the diaphoresis is more marked and the decline of temperature more rapid. Quinine alone will not do this if the temperature is over 100° F., and still rising. Dr. Prout gives a full dose at once, repeating in an hour or hour and a half, and if required another dose may be given. Of course, during the intermission quinine should be given freely.

In *typhus fever* it shortened the delirium and acted well upon the nervous disturbances. In all kinds of neuralgia it is very useful, and especially in hemicrania, lancinating pains of locomotor ataxia, general nervousness, and facial and sciatic neuralgia. In epilepsies at the menstrual period, antipyrin causes some improvement. In other epilepsies it did not avail much. In alcoholic delirium it caused sleep, whilst in paresis and dementia it was valueless. In sea-sickness it is of little value. Locally it arrests hemorrhage. It is especially suited for the fever of children where the thermal changes are rapid and can be checked by the quick action of this drug.

Diabetes.—Germain Seé has made a series of experiments upon animals, in which he produced an artificial glycosuria. He found that antipyrin in a remarkable degree depressed the excitability of the central nervous system, and at the same time lessened the excretion of solids and water of the urine. Hence there can be no doubt that the metabolism of the entire body is retarded. In doses of forty-eight grains divided into three parts, it caused rapid improvement in three to twenty days, the urgent symptoms passing off and the sugar falling to a few grammes or entirely disappearing. Various complications, as boils, eczema, pruritus and neuralgia, disappeared at the same time. Diminution of obesity was usually the first sign of recovery. When the drug causes loss of appetite, puffiness of eyelids or a feeling of tension in the face, then it is to be discontinued. It is not advisable to continuously use antipyrin in diabetes more than twelve days, an interval of several days being allowed before it is resumed. The antipyrin and dietetic treatment can be alternated. This drug may be combined with bicarbonate of soda, one part of the latter to two parts of the former. In diabetes insipidus it has been found to have much value.

Subcutaneous Use.—Subcutaneously it has rapidly and permanently relieved the chest pains of phthisis, the stabbing pains of pleurisy, pains of muscular rheumatism and asthmatic attacks.

Cerebro-Spinal Meningitis.—Here it has been used with much benefit, allaying the terrible pain and favorably influencing the course of the disease. It was given in fifteen grain doses three times during the evening and night.

Sunstroke.—It is advised in sthenic forms to give hypodermically a large dose of the drug, to be repeated if necessary.

Chorea and Tetanus.—In a patient unable to sleep from chorea, ten grain doses of antipyrin every four hours caused him to

sleep well, and in three days the choreaic spasms were cured. In tetanus it has acted better than chloral or bromides. These doses should be carefully watched.

Chronic Urticaria.—In 8 grain doses daily, it acted perfectly.

Pertussis.—Windelschmidt, of Cologne, states that it reduced the duration of the disease to two or three weeks. To do this, it must be employed in the beginning of the disease.

Angina Pectoris.—In this disease, when combined with digitalis, and given three times daily, it proved of great value. Both drugs must be given in large doses.

Erysipelas.—When given internally it caused a marked decrease of fever, a great improvement of the patient's subjective state, and a cessation of the spreading of the disease.

Antigalactagogue.—It is reputed to have this power, and observations seem to confirm this statement.

In *ciliary neuralgia,* due to eye diseases, it has proved of much value.

Incontinence of Urine.—Two doses of 5 to 10 grains given at 6 and 8 P.M. arrested the incontinence, and in a few days cured it. It is recommended that it be given at intervals and continued for a long time. In chronic ulcers and hemorrhoids it was found to be very beneficial when dusted upon them.

Sciatica.—The subcutaneous injection daily of six grains of antipyrin and one-eighth of a grain of cocaine has resulted in greatly modifying the affection.

Nasal Troubles.—A solution (16 grains to ounce) of antipyrin when sprayed into the nose possessed hæmostatic properties, though inferior to cocaine. It may be used upon the nasal mucous membrane with temporary relief for occlusion from engorgement of the turbinates, and with sedative effect upon irritable states, and is most effective where the element of irritation exceeds that of inflammation. It presents an advantage over cocaine in not producing local numbness and dryness, and in the absence of the sleeplessness and headache caused by cocaine. In certain cases of hay-fever, in which an agent for relief is used for long periods, antipyrin as a nasal spray is less likely than cocaine to produce constitutional disturbance or to lead to a habit. Antipyrin also causes more smarting than cocaine, and is unequal to relieve severe inflammation or extreme occlusion of the nares. It may be combined with a one-half per cent. solution of cocaine as a nasal spray, increasing the action of the latter.

Dose.—The dose of antipyrin is 10–20 grains. It is best to commence with 10 grains, and repeat in one to two hours with a large dose, about 15 grains. Three grains are sufficient for a child two years old, not to be repeated more than once daily. To disguise the taste of antipyrin, syrup of orange peel or peppermint is suitable. It often causes an eruption like measles, scarlatina or urticaria, sometimes accompanied by an intense and painful pruritus.

It causes nausea more often in women than in men. This happens even when given by the rectum, thus indicating a central cause for it. The rash occurs chiefly in about ten per cent. of typhoid and phthisical cases, more often after continued use, though in some cases after a brief period and minimum dose. In exceptional cases it appeared after an interval of only five minutes to half an hour. As a rule the exanthematous eruption remains from one to three days, but may be present for a week or more, and it is quite independent of the amount given. The rash is in the beginning chiefly local, but may spread over the whole body. It is most frequently erythematous in character, but may resemble measles, scarlet fever, urticaria, and may occur in different forms in the same individual at various times. The solution of antipyrin for subcutaneous use is of fifty per cent. strength, made with boiled distilled water, which is filtered several times. A syringeful of 8 grains is given, but oftentimes one-half the quantity is sufficient. No bad effects from the antipyrin were observed, but locally the injection causes in all cases some burning pain, which is often intense. This might be relieved by a small amount of cocaine. The effect of the injection appears in a minute and lasts six hours.

Idiosyncrasies to the drug are not uncommon, and small doses may cause great alarm. A quantity well borne at one time may cause dangerous symptoms at another time.

Contra-indications.— It is contra-indicated — (1) during a menstrual period suspending the flow, a statement not confirmed by my experience; (2) in cardiac weakness; (3) in diphtheritic affections with myocarditis; (4) after exhausting hemorrhages; and (5) in the last stages of tuberculosis.

Incompatibles.—It is incompatible with preparations of Peruvian bark, precipitating the active principles. With chloral it causes the solution to have a milky aspect which clears up by the precipitation to the bottom of an oily liquid, having the taste neither of antipyrin nor of chloral, but of coriander seeds.

It is also incompatible with carbolic acid, hydrocyanic acid, nitric acid, tannin, iodide of arsenic, sulphate of copper, sulphate of iron, mercuric bichloride, infusion of uva ursi, permanganate of potash salicylate of sodium, syrup of iodide of iron, tincture of chloride of iron, tincture of catechu, tincture of iodine, tincture of kino and rhubarb. Antipyrin and sweet spirits of nitre form iso-nitroso-antipyrin. It is formed by the free nitrous acid in the nitre acting upon the antipyrin. Iso-nitroso-antipyrin crystallizes in small, grayish-blue crystals which are not poisonous.

Toxicology.

It causes dizziness, tightness and dryness of the throat, huskiness of voice, tingling and burning of gums, coryza, sneezing, œdema of face and eyelids, conjunctival congestion, dilatation of pupil, loss of vision, vomiting, hæmatemesis, jactitation, epileptiform convulsions, deep coma, arythmia of heart, increase of pulse and respiration followed by a slow tense pulse and dyspnœa. It often is followed by pricking of the skin, erythema, urticaria, herpes, sudamina and subnormal temperature. Gastro-enteritis has also ensued from its use. Several deaths are reported; thus, a girl æt. 10 died of two doses of 10 grains each; and a woman with puerperal fever after 15–30 grains. Upon post-mortem the liver was found to be granular and fatty.

Antidotes.—In light degrees of antipyrin poisoning, caffein has been given to elevate the muscular irritability of the heart and to excite the nerve centres.

ANTIFEBRIN.

This is a white, crystalline substance without odor, and causes a slight burning sensation on the tongue, is soluble only in 189 parts of cold water, more soluble in warm water, freely soluble in alcohol, ether and chloroform.

Upon animals, after a short period of excitation, it produces collapse, general anæsthesia and analgesia. It interferes with the conduction of motor and sensory impulses, decreases the reflex activity, which is followed by paralysis, coma and death. Large doses reduce the hæmoglobin to methæmoglobin.

The red corpuscles become granular, partly dissolved, do not form rouleaux. The amœboid movements of the white corpuscles are arrested by it. It increases arterial tension and narrows the capillaries, the pulse becoming less frequent. Large doses depress

the heart and cause collapse. It causes cyanosis, but it is not a serious symptom, soon passing off after the cessation of the administration of the drug. It rarely produces a cutaneous rash, but sudamina and erythema may occur with sweating. The diaphoresis is not as profuse as is seen after antipyrin. Chilliness is sometimes noted when the temperature begins to rise, but rigors and shivering are less common than after kairin, thallin or antipyrin. It produces a fall of temperature within an hour, which reaches its maximum in two to four hours, and the effects of a single dose last from three to six hours. Respiration is but little affected by ordinary doses, but toxic doses make it frequent and then irregular, and finally it ceases. It is a moderate diuretic, but not irritant to the kidneys. It increases the elimination of urea.

One of my students, Dr. Evans, found in animals that it reduces the temperature by diminution of heat production and increase of dissipation.

Therapeutics.

Epilepsy.—When given continuously it reduces the number of fits from twenty-five to seventy-five per cent. as compared with other periods of bromide treatment alternating with a tonic treatment. It was well borne, producing no apparent mental or physical depression or skin eruption.

Mania.—In the typical attacks of excitement and even violence which occur in tabes and dementia paralytica, antifebrin acted as a rapid calmative, producing repose and lessening of the paralytic attacks.

Tonsillitis.—Dr. Sahli gave four to seven grains for a violent attack, and within a quarter of an hour all headache and pain on swallowing or mastication completely disappeared. On the next day there was a slight attack of pain, which was relieved by antifebrin. His subsequent experience confirmed this statement. In the laryngeal spasms of tabetics it has been found quite useful, aborting them.

Ulcers.—In obstinate irritable ulcers (xx gr. to ounce of vaseline), it soothes pain and subdues inflammation. In psoriasis, combined with some mercurial preparation, it acts quite well. Locally in erysipelas, eczema, herpes, urticaria and other irritations, it is a useful adjunct.

Fever.—The action upon temperature begins about an hour after its ingestion and reaches its maximum in about four hours, and passes off in three to ten hours. A dose sufficient to cause a high

fever to descend to normal, keeps the temperature depressed from six to eight hours. The fall of temperature is accompanied by reddening of the skin and great hydrosis. The subsequent ascent of temperature is not accompanied by chills. Simultaneously with the fall of temperature ensues a diminution in the frequency of the pulse, accompanied by an increase in the arterial tension. It causes neither nausea, vomiting nor diarrhœa. The single symptom which was disagreeable was the marked cyanosis of the face and extremities. The fall of temperature is longest and most marked in typhus and typhoid, and intermittent, less marked in pneumonia and pleurisy, and still less in puerperal fever. It is of considerable value in the lightning pains of tabetics and other neuralgias. In variola it is very useful. In small doses it lessens the evening exacerbation and quiets the nervous symptoms. It causes no exanthem. Antifebrin is preferred in fevers, because it acts promptly, and gradually lowers the temperature. The apyrexia is of considerable length, the ascent of the temperature is gradual, there are no chills, no collapse, and it causes a restful sleep. The quieting action of antifebrin is especially useful in tuberculous cases, as it quiets the evening heat, lessens the disturbing cough, and causes sleep. In sciatica, lumbago, epilepsy and migraine, it causes considerable improvement. Occasionally it has caused cyanosis, rapid action of the heart and respiration, collapse and death.

The dose is two to eight grains.

Toxicology.

A girl took sixty-two grains of antifebrin for headache. Immediately after the dose she experienced nausea, eructations, later pains in region of stomach and copious vomiting of a greenish, watery fluid. These symptoms were followed by cyanosis, at first of the lips, later of entire face, hands and feet, whilst the skin of the body was pale and very cold, pulse weak, almost imperceptible, but frequent, 140 per minute; respirations shallow, rapid; patient almost unconscious. Later symptoms of cerebral irritation, dilatation of pupils, muscular twitching of the face, gritting of the teeth, rigidity of extremities and delirium ensued. She sank into a deep coma, from which she awoke in three hours. Eight hours after the poisoning her senses had fully returned, pulse 84, fairly strong, respirations normal, temperature somewhat subnormal. Pain in stomach, dizziness and cyanosis disappeared in twenty-four hours. In two days the patient was able to leave her bed. In the case of a

child, four grains every two hours during the day caused death the same evening.

PHENACETIN.

It is a white crystalline powder, without taste, almost insoluble in water, easily soluble in hot alcohol. Upon animals it accelerates the respiration, causes vacillating gait, sleepiness, vomiting and cyanosis. This discoloration of surface is due to methæmoglobin. It has no depressing action upon the heart, but rather a roborant effect. The frequency of the pulse and respiration diminish with the fall of temperature. When phenacetin is given, the temperature gradually begins to fall in an hour, and reaches its lowest point in three to four hours, and is then followed by a gradual rise, the influence of a single dose lasting six to ten hours. With the fall of temperature there is considerable perspiration, but rarely any gastric disturbance rash, cyanosis or collapse. It increases the flow of urine. I found in animals that it reduces temperature by decreasing heat production and heat dissipation.

Therapeutics.

According to Dujardin-Beaumetz, the three phenacetins have excellent antihyperthermic and analgesic properties. Of the three, only two possess therapeutic activity—para and ortho-acetphenetidin.

The ortho-acetphenetidin must be given in larger doses than the para-acetphenetidin. The medium dose of the latter is about 5 grains to 7 grains three times daily. These two salts are devoid of toxic properties, are powerful antithermics, and very active analgesics, and ought to be substituted for antipyrin for the following reasons: because (1) they are non-toxic; (2) they act in half the dose; (3) they are half as dear; (4) there is no monopoly. The para-acetphenetidin is quite as powerful as antipyrin and antifebrin; it does not cause the pain in stomach or scarlatina-like rash of the former, nor the cyanosis of the latter. However prolonged may be the administration (and he has given it for months in doses of 15 to 30 grains), he has never observed any bad effect. It has been used for the relief of every form of pain—neuralgia, migraine, rheumatism, tabetic pain—and always with the best results. In hysteria and hysterical pains, phenacetin has seemed to produce better results than the bromides, and in some obstinate cases of nervous insomnia it caused sleep. In diseases of children, in small doses, 1½ to 4½ grains, it has a powerful antipyretic effect without producing any disagree-

able symptoms. The action of phenacetin is mainly a sedative one, causing lassitude, yawning, sleepiness, and in a few cases vertigo, chilliness and nausea. In large doses, phenacetin is a valuable anti-neuralgic, especially against migraine. It acts usually slowly but surely in one to two hours, and for the most part without any untoward after-effects. Hammerschlag uses the following prescription for warding off attacks of migraine, it being more efficacious than phenacetin alone:

℞.—Caffein cit. gr. xv.
Phenacetin gr. xxxj.
Saccharin gr. xv.
M. et ft. capsulæ x.
S.—One capsule before the attack.

In pertussis one-half grain doses in glycerine every four hours is sufficient for an infant aged three months. In this disease it has the advantage of not disturbing the stomach.

Pyrexia.—The time at which the temperature begins to fall is about thirty minutes after the ingestion, and the maximum depression occurs in about three hours. The duration of the reduction is usually four to six hours. The transition of the high temperature to the lower and *vice versa* is a gradual one. After large doses (15 to 20 grains) have been administered, profuse perspiration occurs, but no bad consequences supervene. It does not produce a rash like antipyrin and other antipyretics. If administered continuously, the temperature rises in spite of the drug.

In the first week of typhoid fever, phenacetin repeated for several days caused the greatest relief to the severe pain in the head. It quiets the restlessness and promotes sleep. In great restlessness, high fever, delirium, semi-coma of typhoid, the drug has been of considerable advantage combined with other measures. In typhoid, phenacetin is less dangerous than the other antipyretics.

In rapidity of action, antipyrin, on account of its solubility, comes first, next antifebrin, and last phenacetin. The fall of temperature by phenacetin is more gradual, and the minimum is not reached for three, four, even five hours after the administration of the drug. As regards duration of action, that of phenacetin is longer than that of antipyrin or antifebrin. With respect to certainty of action, antipyrin comes first, then antifebrin, and last, phenacetin. Antipyrin, phenacetin and antifebrin cause an equal amount of perspiration.

Dr. Crombie believes that in India several cases of simple continued fever after a chill or exposure to the sun are brought to a sudden termination by their use, which causes profuse sweating and a cessation of symptoms. He also states that in typhoid fever with a temperature of 103° F., where you cannot use the cold pack, the choice lies between phenacetin and antifebrin. If, you are cautious and wish to avoid collapse, he advises phenacetin. If, however, prompt interference is needed, then use antifebrin. According to him, a temperature of 103° F. causes the arrest of gastric digestion and absorption. The perspiration might be thought to be a drawback, but fall of temperature brings a feeling of relief, which the patient is grateful for. According to him, phenacetin has one peculiarity not shared by the other antipyretics—that is, it has a soporific and soothing effect in slight feverishness with insomnia. In heat apoplexy, sunstroke and hyperpyrexia, antipyrin is indicated; in temperatures of 103-105° F. antifebrin or phenacetin is used.

Articular Rheumatism.—Here antipyrin and antifebrin are valuable nervines, antipyrin being the better of the two. For the fulness of the head from the excessive use of alcohol, doses of phenacetin are followed by the best results. In insomnia, when this is not due to pain, phenacetin is of extreme value, given in a little water.

Toxicology.

Dr. Hollopter reports the following case: Mrs. W., aged 30, married, anæmic, nervous temperament, had been for years a sufferer from chronic pelvic trouble and persistent neuralgia of migraine form. She had taken antipyrin and antifebrin for it in doses of 15 grains four or five times daily without any characteristic symptoms. She did not receive much benefit from their use. He then gave her 7½ grains of phenacetin every two or three hours. Six hours after leaving his patient he was urgently requested to see her, and found her in a state of collapse, severe precordial pain, great dyspnœa, lividity of the nails, lips, conjunctiva and the whole surface; great restlessness, inability to lie down or stand; was supported in a semi-recumbent position. Involuntary movement of bowels occurred once, pulse below normal, slow, soft; cold perspiration, pupils slightly dilated. She remained in this condition for about ten hours, slowly improving under the use of ammonia and alcoholic stimulation. The blueness did not fade away for more than three days. Convalescence was very slow, the patient not being able to be around her room for over a week. About 22 grains were taken during the six hours.

EXALGIN.

Binet states that it diminishes motor power in all animals. It produces local paralysis in the muscles where injected, arrests the heart, diminishes oxyhæmoglobin, and interferes with the oxygenation of the blood. Subcutaneously it produces within one to two minutes clonic epileptiform convulsions and profuse salivation. The attacks of convulsions are separated by periods of relapse, in which there are more or less cyanosis, difficulty of breathing and agitation. The convulsions are of cerebral origin. The temperature is rapidly reduced by the injection, the reduction appearing within ten minutes after the injection, and attaining its maximum in about three-quarters of an hour. Small doses increase arterial tension. Death is partly produced by want of oxygenation of the blood, as it shows an abundance of methyl-hæmoglobin. The animal can become accustomed to the drug, so that subsequent injections must be larger. It causes death by respiratory paralysis. It reduces the temperature, but has little action in lessening heat production.

Therapeutics.

Sixteen to twenty grains of exalgin will dissolve in half a drachm of alcohol, and to this solution you can add 3–4 ounces of water, and the solution remains perfectly clear. Four to six grains given at once, or 6–12 grains in two doses during twenty-four hours, cause marked analgesia in all forms of neuralgia, including visceral neuralgia. Its action is most marked in pure facial neuralgia. No gastro-intestinal irritation has been noticed after its administration. It is also of much benefit in dental and congestive neuralgia and migraine. Exalgin is apt to cause a vertigo sort of drunkenness like quinine, and a rash and cyanosis, with sweating. Dujardin-Beaumetz, its introducer, considers it inferior to antipyrin, chiefly owing to its sparing solubility. The dose of exalgin is 4–6 grains, but 1 will be better to start with every four hours. In lightning pains of locomotor ataxia, or lumbago and muscular rheumatism, it is useful. This drug cannot be used for any length of time on account of its destructive action upon the blood.

Toxicology.

In a girl, aged 24, a case of myelitis, from June 3d until June 8th, exalgin was given in two grain doses three times daily. The dose was then doubled, but even this amount failed to give relief. It was increased to 6 grains on June 10th three times daily,

and continued until June 17th, when symptoms of poisoning first set in. At 10.30 A.M. on the 17th, the lips and cheeks were noticed to be blue, the pulse small and compressible, but not rapid, the temperature normal. Though there were no very urgent symptoms, the drug was discontinued, and two drachms of brandy ordered every hour. The patient stated that the medicine made her feel sick and giddy, that her sight was indistinct, and that there was a feeling of weight at the epigastrium. At 3.30 P.M. a few inhalations of amyl nitrite were given, which considerably emphasized the blueness and caused marked dilatation of the vessels. The cyanosis continued to increase, and at 3.45 P M. the patient vomited, after which it became still more marked. At 4.10 P.M. her nails, lips and cheeks were deeply cyanosed; frothing saliva was escaping from her mouth; she was delirious and appeared to recognize no one. Her feet were not blue or cold. Temperature 99.8° F., pulse 144, very small and regular. She was then given strychnia and digitalis, and at 9 P.M. her condition was fairly normal, save slight cyanosis. In other cases a sudden collapse came on, an inability to speak or move, they felt suspended in the air, or lost all feeling, their head felt as if greatly expanded, and gaspings for breath were observed.

PYRODIN.

It is a white, crystalline powder, sparingly soluble in cold water, and has very little taste. In large doses the heart's activity is lessened and the arterial tension reduced by an action on the main vasomotor centre. It depresses spinal reflex action. Repeated doses cause jaundice, due to an action upon the hæmoglobin. In doses of 8–12 grains the temperature is réduced markedly in two to four hours, when a slight rise occurs, followed by a second reduction, so that the effect of one dose may last all day. The antithermic effect is accompanied by profuse diaphoresis, but no collapse, nausea or vomiting. It should be given in small doses and only once in twenty-four hours. It is a dangerous drug, and I cannot advise its use.

It should not be continued for more than a few days, as it may cause jaundice, hebetude, albuminuria and hæmoglobinuria and death. Doses of 3–4 grains have been given to children. It has been used in pneumonia, scarlet fever, typhus and typhoid fevers.

Hydracetin, the purified principle of pyrodin, is five times stronger, and causes cyanosis of face, chills, reduction of tempera-

ture, abundant sweats, arrest of pulse and respiration, with collapse. In rheumatism of the joints, hydracetin exercises a powerful antipyretic action in small doses of ¾–3 grains daily. The dose recommended is 1½ grains in two doses of ¾ grain. In psoriasis a ten per cent. ointment of hydracetin acted very efficiently.

Dr. Canti gave a lad suffering from tetanus about seven grains of pyrodin daily; on the third day the urine was intensely dark-red in color, and was found to contain methæmoglobin and urobilin, under a diet consisting largely of milk and ale. Toxic symptoms disappeared in twelve days, but the patient remained in a state of grave anæmia. The pyrodin did not lower the temperature and had no effect upon the tetanic symptoms. He considers it a powerful blood-poison with a destructive action upon the red blood corpuscles analogous to that of chloride of potassium.

METHACETIN OR PARA-ACETANISIDIN.

It is a slightly reddish powder, of a faintly bitter taste, soluble in warm water, but less so in cold water, very soluble in alcohol.

It is poisonous to rabbits in doses of 45 grains, causing convulsions and death.

Upon the lower animals it reduces the temperature, heat production and heat dissipation.

Therapeutics.

When given in moderate fever (100.4–102° F.) in doses of from 5–6 grains, it brought the temperature down to normal, but with higher degrees of pyrexia, 6–9 grains had to be administered. It causes a fall of three to five degrees in a few hours, with profuse perspiration. It resembles antipyrin in its action. In children in doses of 2–3 grains it reduced the temperature in a gradual manner, and it remained so for several hours and then gradually ascended. In phthisis, with an evening temperature of 104–104.6° F., doses of 6 to 7 grains in the afternoon between 2–3 P.M prevented a rise of temperature above 100.4° F. The effects ensued rapidly on account of the drug's solubility, sometimes in fifteen to twenty minutes, certainly after half an hour. The fall of temperature was gradual, and reached its minimum in about three hours; it remained there about an hour, and then a more rapid rise ensued, sometimes with a rigor. The drug is best given in phthisis between 3–4 P.M., if it is to be administered but once a day. It occasionally has an unfavorable influence upon the heart, slight collapse ensuing after

seven grains. The lowering of the temperature is accompanied by profuse sweating. Its use is not followed by either hæmoglobinuria or glycosuria. Dr. Seidler found in moderate fever that doses of ½–¾ grains were sufficient to reduce the temperatuue to normal. He has found it to act well in acute and subacute rheumatism, decreasing the pain, fever and swelling. As an anti-neuralgic it was less efficacious. The dose is one-half that of phenacetin, seven and a half grains being sufficient for an adult.

ANTITHERMIN.

Physiological Action.

By the jugular, antithermin decreased the pulse, but did not materially affect the arterial tension. It reduces temperature with a diminution of heat production and heat dissipation.

Therapeutics.

It has an action similar to antipyrin although weaker.

ANTISEPSIN.

Physiological Action.

In small doses upon the lower animals it causes mydriasis, reduction of temperature, cold tremors accelerated peristalsis and diuresis. In toxic doses it produces spasms, intense mydriasis, depression of temperature, reduction of heart's frequency, disturbed respiration, hæmoglobinuria and glycosuria. It causes death by cessation of respiratory movement, the heart being the last to die.

Therapeutics.

Dr. Cattani states that in doses of about a grain four times daily, it reduced the temperature from 1.8–3.6° F. When employed in the pyrexia of phthisis pneumonia or typhoid, the effects were practically the same. If the dose was large the tendency to cyanosis was greater than with antifebrin. This cyanosis from methæmoglobin was evanescent and the only unfavorable accompaniment of its administration. In neuralgia it acted like antifebrin. The drug is principally remarkable for the effect of its topical application to non-bleeding wounds, and this peculiarity suggested its name. When applied to wounds and ulcers it was observed that rapid improvement ensued, the granulations flattened down, and cicatricial spots appeared. It also relieved the pain and itching. It is applied as a powder.

VALUE OF ANTITHERMICS IN TYPHOID FEVER.

Temperature is only one section of fever, a process which is very extensive and contains many other problems to be solved. At present there are two views about the temperature of fever—one that high fever is a salutary process, that either by its temperature or by making the tissues uncongenial, it destroys the bacteria. It seems to me that the organisms of fever, like those outside the body, have a definite cycle of life, and no antithermic treatment is able to abridge that cycle one minute, or shorten the duration of a typhoid fever one day; that neither a high nor subnormal bodily temperature has any influence upon the biological history of a microbe of typhoid fever. The other theory is, that high temperature is the dangerous element in fever, and must be combated at all hazards. Against this theory, a temperature of 107° F. may exist for days in relapsing fever, and yet cause no ill result.

Dr. Langstaff* relates a case of typhoid fever ending in recovery with a continuous temperature of 104° F. for seventeen days. A temperature of 107° F. in typhoid fever, in my experience, would end the case in a few hours, not from the high temperature, but from the profound disturbance of the nervous system. The fact is, that it is not the high temperature in itself, but the great disturbance of the thermotaxic centres, and necessarily of the other parts of the nervous system, which is the danger. High temperature is only one sign of this great disorder of the nervous system. I have seen a case of typhoid fever about its sixth day where the fever poison so affected the respiratory centre that the respirations were reduced to four per minute, and they remained at this rate till death ensued, at the end of twenty-four hours. In this case the average temperature throughout the disease was not high. I have seen cases of typhoid fever where the temperature remained subnormal for the greater part of the time, yet they were highly dangerous. In measles the

* New York *Medical Record*, 1889.

fever continues high—longer than in scarlatina, yet the latter is a dangerous disease when severe. Now we know that quinine has but little effect upon the malarial paroxysm when given during it, but how great its effect when given before! Here the quinine so acts upon the thermotaxic centres that the malarial microbes and their chemical products are powerless to displace the hold of quinine. The preceding researches show that quinine has an action on the thermotaxic mechanism while the malarial bacteria are passing through their life history. Quinine prevents the action of them or their products, and the phagocytes may develop and destroy them. Now what can be expected of the antithermics excepting quinine? That like it they act upon the thermotaxic centres is proved by the researches previously related, that they do not act alike or in the same degree is shown by the fact that the modern antithermics are powerless to prevent malarial paroxysms. Looking at the typhoid fever bacterium as passing through its life cycle, these antithermics are powerless to kill it, yet these drugs modify the temperature of the body.

All these antithermics are nervous agents, and are beneficial to quiet the nervous system in hyperpyrexia, not necessarily by reducing the pyrexia, but by their quieting influence upon the nervous system in other respects. But it must be only in a few periods in the fever that they are permissible, as almost all have a depressing influence upon the heart. In the "thallinization" of Ehrlich it does not appear that the fever is shortened a day, although the temperature was kept almost completely in abeyance. Neither was the mortality lessened, as far as I can see. They were certainly mild cases, or the action of the thallin upon the heart and kidneys would have made the fatality high. The researches upon the thermopolypnœic centre show how intimate is the relation of the peripheral endings of the sensory nerves in the skin to that thermotaxic centre. Now, it is highly probable that the other thermotaxic centres are connected with the same sensitive apparatus. In this manner baths, not so much by their temperature as by their action upon the sensory nerves, influence the thermotaxic centres, so as to restore their original vigor. If you shave all the hair off a rabbit and paint him with a gum solution, although the room is very warm, yet his temperature will fall enormously. Here there is only skin irritation and not increased dissipation which is acting upon the thermotaxic centres. In the same manner I believe water, either warm or cold, to act in reducing the temperature of fever.

Dr. Anuschat advocates the employment of warm baths in typhoid fever in place of cold water. He disputes Brand's doctrine that the good effects of the cold bath are due solely to the low temperature, as in that case it would be equally advisable in all acute fevers. He believes the beneficial effect to be due to the water rather than to its temperature. He treated 150 cases, administering three baths daily, from 15–25 minutes each, at 95° F. if the temperature of the body is between 100.4 and 102.2, at 93° F. if the body temperature is 102.2 to 104°, and at 90.5 only if the temperature of the body is higher than 104°. In most cases a perceptible improvement took place in three days with decrease of fever, but the good effect of the warm bath treatment is most plainly seen in the almost entire absence of secondary symptoms, and the much shorter duration of the illness. Of the 150 patients 145 were less than four weeks in bed, and most of them less than twenty-one days. When the temperature of the body falls below 99.5° F., the bath is administered less frequently.

This agent, water, has neither the depressing action of modern antithermics upon the heart nor their irritating action upon the kidneys. For the same reason quinine is to be preferred as an occasional antithermic in the grave hyperpyrexia of typhoid, unless the symptoms denote great cerebral excitation, or the so-called meningitis, when antipyrin is to be preferred. Antipyrin is the least harmful, as it does not act upon the hæmoglobin like kairin, thallin and pyrodin, or cyanose like antifebrin. It is more soluble than phenacetin or antithermin, and less disposed to act upon the heart. As the plan of Brand's cold water treatment is not always readily accessible, I append it:

"The bath-tub shall be placed near the bed, and shall contain a sufficient quantity of water so that the patient when immersed in it shall be completely covered up to the neck. The temperature of the water should not exceed 78° F. Tripier and Bouveret distinguish in this regard three varieties of cold baths—baths with a temperature of 71–75 F., of 64–68 F., and 57–59 F.—and they regulate the temperature of the bath by the intensity of the fever and the resistance to refrigeration. Before carrying the typhoid patient to the bath-tub, and in order to diminish the trying and painful sensation of cold, the abdomen is rubbed with the water of the bath. Then the patient is placed in the bath, and all the time that he remains there the head is showered with ice-cold water. It is understood that the hair shall have previously been cut short in order to render

these affusions more active. Brand recommends also to rub the belly and back of the patient during the time of the bath. The patient is kept in the bath about fifteen minutes, and in certain cases the bath may be prolonged to twenty minutes. At the end of this time the patient is taken with shivering and chattering, and is then removed to his bed, and his lower limbs are covered with blankets. As for the rest of the body, in summer, only a simple sheet is employed, and in winter a sheet covered by a woollen blanket. At the end of twenty minutes the temperature is taken, and, during the period of comfort which ensues, some nourishment is given. Every hour the temperature is taken anew; and when the mercury resumes its ascending march and reaches 102–103° F., whether during the day or night, the patient is again plunged into a cold bath. Brand has fixed at about three hours the interval which should elapse between the baths, but this period may be made much shorter and reduced to two hours or one hour and a half, if there be high-fever heat and great resistance to refrigeration. Brand insists, also, that in the interval of the baths the nurses should keep constantly applied over the abdomen of the patient compresses wet with cold water, and renewed as fast as they become warm. It is well on the inception to resort to cold ablutions with towels (not sponging). Friction aids heat elimination by dilating the cutaneous vessels, and the shock refreshes the nerve centres. Then the patient grows accustomed to the more energetic bathing, which may be opened with the half-bath combined with gentle chafing, and gradually culminate in the full bath at 65° F. The patient when taking the bath, and at all times, should be well supported with such nourishment as is suitable for his condition—milk, wine, broths, peptonoids, etc. No other treatment is employed." For this treatment to be successful, it must be applied from the very onset of the fever. In proportion to the tardiness and lateness of its inception, the chances of success are lessened.*

* Whittier, *Boston Medical Journal*, 1889.